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Improving Oral Bioavailability of Sorafenib by Optimizing the "Spring" and "Parachute" Based on Molecular Interaction Mechanisms

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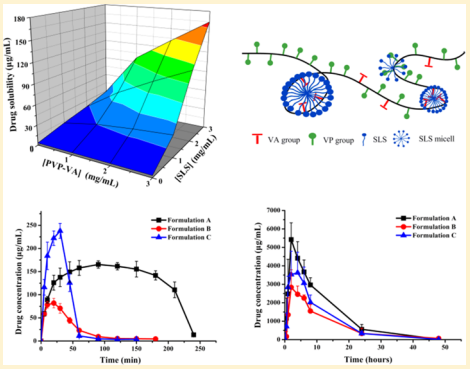
ABSTRACT: Sorafenib is a clinically important oral tyrosine kinase inhibitor for the treatment of various cancers. However, the oral bioavailability of sorafenib tablet (Nexavar) is merely 38−49% relative to the oral solution, due to the low aqueous solubility of sorafenib and its relatively high daily dose. It is desirable to improve the oral bioavailability of sorafenib to expand the therapeutic window, reduce the drug resistance, and enhance patient compliance. In this study, we observed that the solubility of sorafenib could be increased ∼50-fold in the coexistence of poly(vinylpyrrolidone-vinyl acetate) (PVP-VA) and sodium lauryl sulfate (SLS), due to the formation of PVP-VA/SLS complexes at a lower critical aggregation concentration. The enhanced solubility provided a faster initial sorafenib dissolution rate, analogous to a forceful "spring" to release drug into solution, from tablets containing both PVP-VA and SLS. However, SLS appears to impair the ability of PVP-VA to act as an efficient "parachute" to keep the drug in solution and maintain drug supersaturation. Using 2D ^{1}H NMR, ^{13}C NMR, and FT-IR analysis, we concluded that the solubility enhancement and supersaturation of sorafenib were achieved by PVP-VA/SLS complexes and PVP-VA/sorafenib interaction, respectively, both through molecular interactions hinged on the PVP-VA VA groups. Therefore, a balance between "spring" and "parachute" must be carefully considered in formulation design. To confirm the *in vivo* relevance of these molecular interaction mechanisms, we prepared three tablet formulations containing PVP-VA alone, SLS alone, and PVP-VA/SLS in combination. The USP II *in vitro* dissolution and dog pharmacokinetic *in vivo* evaluation showed clear differentiation between these three formulations, and also good *in vitro*−*in vivo* correlation. The formulation containing PVP-VA alone demonstrated the best bioavailability with 1.85-fold and 1.79-fold increases in C_{max} and AUC, respectively, compared with the formulation containing SLS only, the poorest performing one. Despite its forceful "spring", the formulation containing both PVP-VA and SLS showed a moderate bioavailability enhancement, due to the lack of an efficient "parachute".



KEYWORDS: *sorafenib, bioavailability, poorly water-soluble drugs, molecular interaction, polymer−surfactant complex*

1. INTRODUCTION

Sorafenib (Nexavar) is an orally bioavailable, small molecule inhibitor of multiple tyrosine protein kinases (VEGFR, PDGFR, and Raf kinases, etc.) that are components of signaling pathways controlling tumor growth and angiogenesis.[1,2] Researchers have shown that sorafenib has antitumor activity across a variety of tumor types, including renal cell, hepatocellular, breast and colorectal carcinomas, and melanoma in the preclinical setting.[3,4] Sorafenib has been approved for the treatment of primary kidney cancer (advanced renal cell carcinoma), advanced primary liver cancer (unresectable hepatocellular carcinoma), and thyroid cancer.[5] In particular, sorafenib is the only medicine systemically administrated that showed clinical effectiveness toward hepatocellular carcinoma, a very common form of cancer with poor prognosis in some southeast Asia and Africa countries, due to prevalence of hepatitis B and hepatitis C transmission.[6]

Sorafenib has a high daily dose of 400−800 mg, yet a very low and pH dependent water solubility of ∼1.7 μg/mL in water, 34 μg/mL at pH 1.0, and 13 μg/mL at pH 4.5.[5,7] Together with a high permeability through the gastrointestinal membrane, it is classified as a BCS II compound.[8] Sorafenib is also very lipophilic (LogP = 3.8) and has a strong crystal lattice (T_m = 205 °C).[9,10] The marketed sorafenib oral tablet, Nexavar, containing crystalline sorafenib tosylate as the active pharmaceutical ingredient (API), provides an oral bioavail-

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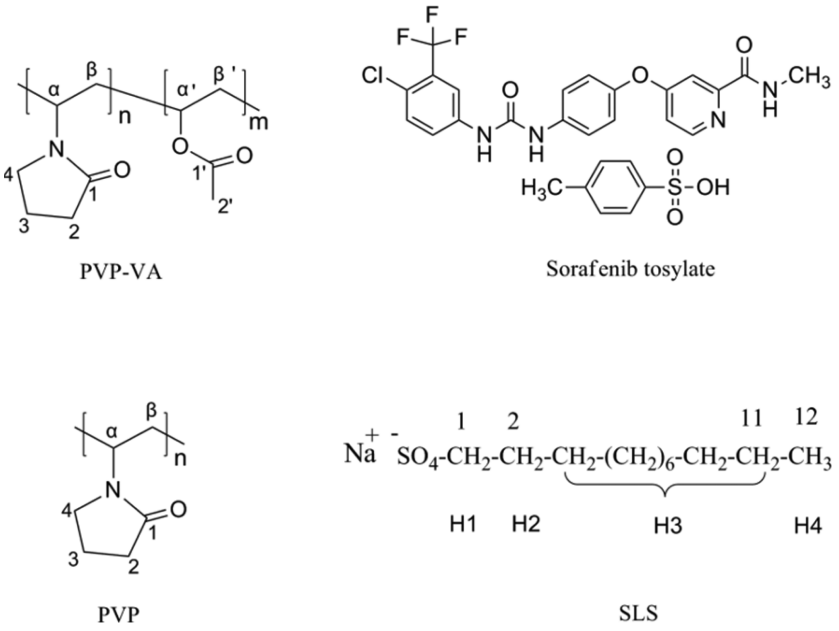

Figure 1. Chemical structure of sorafenib, polyvinylpyrrolidone (PVP), poly(vinylpyrrolidone-*co*-vinylacetate) (PVP-VA), and sodium lauryl sulfate (SLS).

ability of 38−49% relative to an oral solution formulation at the dose levels between 100 and 400 mg.[7] Food and pH have a significant effect on bioavailability of sorafenib due to the aforementioned physicochemical properties: with a high-fat meal, sorafenib absorption could be reduced by approximately 29% compared to administration in the fasted state.[7] Any anti-acid medicine such as proton-pump inhibitors could also decrease its bioavailability, as observed in a phase II clinical study.[11] Subtherapeutic concentration not only will lead to poor anticancer responses to the treatment but also might fuel the emergence of drug resistance, a common cause of failure for cancer chemotherapy.[12] Obviously, strategies to improve the solubility and bioavailability of sorafenib while reducing its pH and food effects are of substantial clinical benefit.

Various technologies are widely used to enhance the solubility and bioavailability of poorly soluble small molecule drugs, including salt/prodrug formation,[13,14] particle size reduction,[15,16] solutions in nonaqueous vehicles,[17] and high energy/metastable drug delivery systems such as amorphous solid dispersions etc.[18,19] When these formulations dissolve, it is not unusual that supersaturation occurs and is further extended for various time periods, depending on the formulation and the dissolution medium.[20] An elevated and extended drug supersaturation in the gastrointestinal (GI) tract over a prolonged time period could evidently maximize the bioavailability. The producing and maintaining of drug supersaturation are analogous to the "spring" and "parachute":[20] where "spring" refers to the initial dissolution of the drug from the dosage form, determined by the drug solubility and surface area; while "parachute" refers to the prolonged supersaturation, often achieved through appropriate selection of excipients that could prevent drug crystallization and retard drug precipitation.[21−23] It is conceivable that a formulation with optimally designed "spring" and "parachute" could offer the most desirable *in vivo* performance with the highest bioavailability.[20,24]

In this study, we demonstrate that the molecular interactions between sorafenib, poly(vinylpyrrolidone-vinyl acetate) (PVP-VA), and sodium lauryl sulfate (SLS) play critical roles in controlling the solubility (i.e., the "spring") and the supersaturation (i.e., the "parachute") of sorafenib and, eventually, the *in vivo* bioavailability. We observed that sorafenib solubility increased ∼50 times with PVP-VA and SLS used in synergy due to the solubilization of sorafenib by the PVP-VA/SLS complexes. However, addition of substantial amount of SLS into PVP-VA containing formulation reduced the ability of PVP-VA to maintain sorafenib supersaturation and, thus, could jeopardize the bioavailability of sorafenib despite an increased solubility. We conclude that the drug−excipient and excipient−excipient interactions could have profound impacts both on the drug release mechanism from the dosage form and the drug precipitation kinetics from supersaturation. Therefore, careful studies must be performed to achieve the optimal balance between the "spring" and the "parachute" and, ultimately, the optimal oral bioavailability.

2. MATERIALS AND METHODS

2.1. Materials. Sorafenib tosylate was provided by Qilu Pharmaceuticals, Inc. (Shandong, China). Sorafenib (free base) was bought from Ouhe Company (Beijing, China). Unless specifically stated, the term "sorafenib" in this paper refers to the free base. PVP-VA (Kollidon VA 64) and PVP (poly(vinylpyrrolidone), Kollidon 30) were provided by BASF Chemical Company Ltd. (Ludwigshafen, Germany). The chemical structures of sorafenib tosylate and polymers are summarized in Figure 1. All buffer salts used for dissolution medium and acetonitrile (HPLC grade) were purchased from Beijing Chemical Works (Beijing, China).

2.2. Solubility Measurement of Crystalline Sorafenib Tosylate. Solubility of crystalline sorafenib tosylate in FaSSIF,[25] in the presence of either polymer or SLS, or the combination of the two, was determined by suspending an excess amount of crystalline drug in the solution, followed by vortexing (1 min), sonication (30 min), and then shaking using an orbital shaker (37 °C, Burrell wrist action shaker, model 75) for 24 h. The suspension was subsequently centrifuged at 15,000 rpm (Changsha Pingfan Co., Ltd., TG16W, China) for

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3 min, and the drug concentration of the supernatant was determined by HPLC/UV−vis. The concentration of coexisting polymer and/or SLS is 1, 2, or 3 mg/mL.

2.3. Sorafenib Supersaturation Kinetics in the Presence of Different Excipients. Supersaturation kinetics of sorafenib in FaSSIF or water containing different excipients were determined using a reported method.[25] Briefly, PVP-VA or PVP was predissolved in FaSSIF solution at concentrations of 0.3 and/or 3 mg/mL. DMSO solutions of sorafenib were prepared at 100 or 20 mg/mL. Into each 10 mL of polymer containing dissolution medium was added 100 μL of DMSO drug solution. The solution was then vibrated at 100 rpm using a shaker (37 °C, Burrell wrist action shaker, model 75). After 20 min and 1, 2, and 4 h, the solution was centrifuged (15,000 rpm) for 3 min and the clear supernatant was analyzed for the concentration of drug using high performance liquid chromatography (HPLC) (Shimadzu LC-20AT, Kyoto, Japan). The concentration of polymer was analyzed using HPLC-ELSD methods as reported before.[25]

2.4. Fluorescence Spectroscopy Method To Identify the CMC or CAC of Polymer/SLS Solution. A fluorescence method was used to study the self-assembly of SLS in the presence of polymers at 25 °C. Fluorescence spectra were obtained using a Fluoromax-3 (Horiba Jobin Yvon, Edison, NJ) spectrometer. Pyrene, a hydrophobic fluorescent probe that exhibits different fluorescence characteristics depending upon its self-association status, was added in the SLS/polymer containing aqueous medium at a concentration of 2×10^{-4} M to reveal the self-assembling events. The solutions were filled into cuvettes, and the emission spectra of pyrene were collected when applying an excitation light of 334 nm. The critical micelle concentration (CMC) of SLS or critical aggregation concentration (CAC) of SLS/polymer solution was identified at the concentration where the peak intensity ratio between the pyrene 373 and 383 nm peaks starts to decrease.

2.5. Solution NMR To Analyze the Molecular Interaction between Polymer, Surfactant, and Sorafenib. In order to understand the molecular mechanism governing the interactions between polymer, surfactant, and sorafenib, 2D ^{1}H NMR spectra and ^{13}C NMR spectra of various solutions were collected by a Bruker AV-400 NMR spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany) operating at a proton resonance frequency of 400 MHz. For ^{1}H NMR spectra, the spectra were acquired at 298 K, and the chemical shifts were referenced with respect to HDO (4.735 ppm). For nuclear Overhauser effect spectroscopy (NOESY) study, the mixing time was set to 0.2 s, and a relaxation delay of 3 s was used between the scans. For ^{13}C NMR analysis, all samples contained 10% w/w deuterium oxide and a trace of *p*-dioxane. The latter was used as the internal reference.

2.6. Hydrophobicity of Polymer Functional Groups Determined by Computational Method. We used the software package QikProp[26] (Schrödinger, LLC) to predict the logP values of the vinylpyrrolidone (VP) and vinyl acetate (VA) groups on PVP and PVP-VA, using the default parameters. As a logarithm parameter evaluating the octanol−water partition coefficient of a molecule, logP value can be used to compare the relative hydrophobicity of different molecules or functional groups.

2.7. FT-IR Spectroscopic Investigation of Sorafenib−Polymer Molecular Interaction in Solid State. To further understand the mechanism of drug−polymer interaction in the solid state, FT-IR spectra of sorafenib/PVP and sorafenib/PVP-VA molecular levels mixtures obtained by solvent evaporation were collected and analyzed. Briefly, sorafenib/PVP and sorafenib/PVP-VA (60/40 drug/polymer w/w) amorphous mixtures were prepared by spray drying their acetone solution with a Buchi B-295 spray-dryer (Büchi Labortechnik AG, Postfach, Switzerland). The inlet temperature was 70 °C, and the outlet temperature was ∼40 °C. After spray drying, the obtained materials were vacuum-dried overnight at ambient temperature. The FT-IR spectra of the sorafenib/PVP and sorafenib/PVP-VA mixtures were collected by Fourier transform infrared spectroscopy (Vertex 70, Bruker Optics, Ettlingen, Germany) with a spectral resolution of 4 cm^{-1}. The IR spectra in the wave number range 4000−700 cm^{-1} were recorded for further comparison. As controls, the IR spectra of pure amorphous drug, pure polymers, and physical blends of polymer and amorphous drug (PM) were also collected.

2.8. Preparation of Sorafenib Tablet Formulations. Three types of sorafenib tablets were prepared according to the composition listed in Table 1. Briefly, the crystalline sorafenib tosylate, microcrystalline cellulose (MCC), croscarmellose sodium (CCNa), PVP-VA, etc. were mixed manually using sieves. The obtained powder mixtures were compressed by carver press (C-NE 3888, USA) at a pressure of 400 kgf.

Table 1. Compositions (mg) of Three Tablet Formulations (A−C) for Dog Pharmacokinetic Evaluation

	A	B	C
sorafenib tosylate	137	137	137
PVP-VA	150	0	150
MCC	520	650	500
CCNa	65	65	65
SLS	0	20	20
total weight	872	872	872

2.9. Dissolution Studies of Sorafenib Tablets. The USP II dissolution of various sorafenib tablets was carried out using an USP II apparatus (Automated lab systems, ADT8, U.K.). The dissolution medium was 300 mL of FaSSIF (37 °C). Paddle speed was 75 rpm. At predetermined time points, 0.5 mL of dissolution medium was withdrawn and filtered with 0.45 μm syringe filters. The solution obtained was then further diluted with methanol and analyzed by HPLC/UV−vis.

We also carried out a "pseudo" intrinsic dissolution study of the sorafenib tablets using a homemade device under nonsink conditions. Briefly, tablets with diameters of 11 mm and the compositions listed in Table 1 were first compressed by Carver press. The tablets were then sealed with wax within syringe tubes with only one surface exposed to 20 mL of FaSSIF, which was stirred by a 2 cm magnetic stir bar with the rotation rate of ∼150 rpm. At predetermined time points, the dissolution medium was withdrawn and the drug concentration was analyzed using HPLC/UV−vis. We termed this dissolution setup as "pseudo" intrinsic dissolution because the originally and more strictly defined intrinsic dissolution rates were typically determined under sink condition using a rotating disk to eliminate the contribution from the unstirred layer effect.[27,28] The major purpose of our dissolution setup is to eliminate the impact of powder properties and to be discriminating against different formulations. It is worthwhile to note the differences between this "pseudo" intrinsic dissolution and the "true" intrinsic dissolution, although we will simply use the term "intrinsic dissolution" in this paper to be concise.

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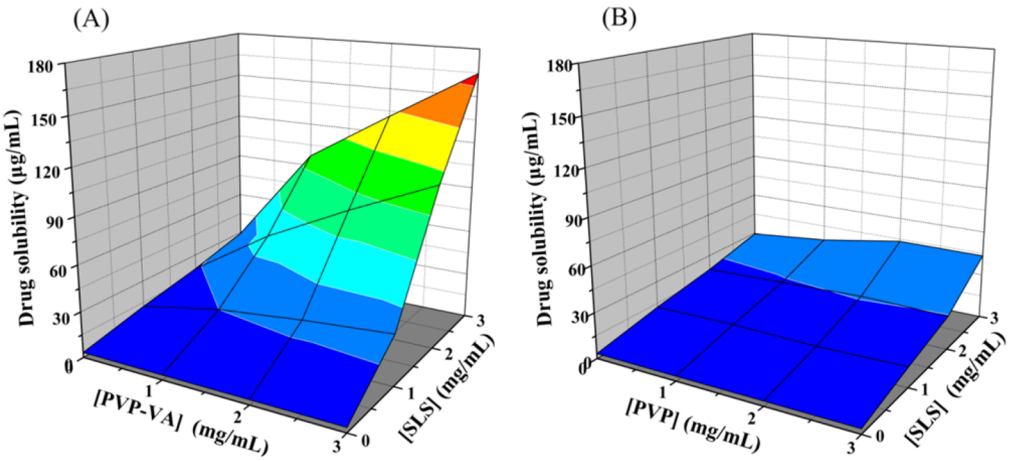

Figure 2. Solubility of sorafenib in FaSSIF (pH 6.5) solution in the presence of (A) SLS and PVP-VA and (B) SLS and PVP at different concentrations.

2.10. Pharmacokinetic Comparison of Sorafenib Tablets in Dogs. The pharmacokinetic performance of the sorafenib tablets (137 mg of sorafenib tosylate, in equivalent of 100 mg of sorafenib free base) was evaluated in male beagle dogs (~10 kg) using a crossover study (n = 3). At least 1-week washout period was ensured between dosing to avoid interference between different formulations. The dogs were fasted overnight prior to each dosing session and were given food again 4 h after dosing. Oral administration of tablets was followed immediately by gavage with 20 mL of water. Blood samples (2 mL) were withdrawn from the cephalic vein predosing, and at 10 min and 0.5, 1, 2, 4, 6, 8, 24, and 48 h after dosing. The samples were then placed in EDTA-containing vacutainer blood collection tubes. The samples were subsequently centrifuged at 400g for 15 min at 4 °C, and the plasma was isolated and stored at −80 °C until HPLC LC/MS analysis (Applied Biosystems, Foster City, USA). The dog pharmacokinetic study was performed in accordance with the standards recommended by the Guide for Care and Use for Laboratory Animals (Institute of Animal Laboratory Resources, 1995) and was approved by the institutional animal care use committee with full consideration to experimental refinement, reduction in animal use, and replacement with *in vitro* methods.

3. RESULTS AND DISCUSSION

3.1. Solubility of Crystalline Sorafenib in FaSSIF with the Coexistence of Polymer and/or SLS. The effect of polymer and SLS on the solubility of crystalline sorafenib is illustrated in Figure 2. Without polymer or SLS, the solubility of crystalline sorafenib in FaSSIF is very low at 3.3 μg/mL. With the addition of PVP-VA or PVP alone, the solubility of sorafenib remains unchanged up to 3 mg/mL polymer concentration. With the addition of SLS alone up to 3 mg/mL, the solubility of sorafenib increased ~9 times, to 29.4 μg/mL. A more dramatic increase of sorafenib solubility was observed when 3 mg/mL PVP-VA and 3 mg/mL SLS coexist: the synergistic effect between PVP-VA and SLS significantly increased the solubility of sorafenib ~50 times, to 164.6 μg/mL. This phenomenon was also observed in PBS solution (data not shown). Interestingly, similar synergistic effect was not observed in the solution where PVP and SLS coexist. With the coexistence of 3 mg/mL PVP and 3 mg/mL SLS, the solubility of sorafenib increased 13 times to 43.3 μg/mL, comparable with the solubility enhancement achieved by SLS alone. Based on these results, and the fact that PVP and PVP-VA differ in the absence or presence of the vinyl acetate (VA) groups, we reasoned that the VA groups played the key role to synergy with SLS, which enhanced the solubility of sorafenib.

3.2. CMC/CAC Values in the Solution Containing SLS and Polymer/SLS. As a surfactant, SLS could self-assemble to form micelles, or assemble surrounding the hydrophobic segments of various polymers. In order to study the assembling behavior of SLS and polymer/SLS systems, a hydrophobic fluorescent dye, pyrene, was added into the solution. The fluorescence peak ratio I_1(373 nm)/I_3(383 nm) was plotted against the SLS concentration, and the bending point of the curve was identified as the CMC/CAC values (Figure 3). Above the CMC/CAC concentration, aggregates with hydrophobic cores formed, within which pyrene concentrated and caused the change in the I_1/I_3 value.

As shown in Figure 3, the CMC/CAC values of the SLS, PVP/SLS, and PVP-VA/SLS systems were 8.0, 2.2, and 1.1 mM, respectively. Obviously, SLS could assemble at a much lower concentration in the presence of PVP or PVP-VA.

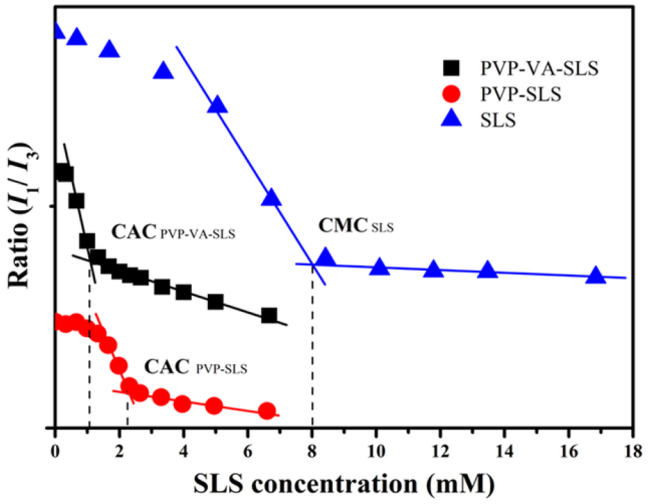

Figure 3. Change of the fluorescence intensity ratio (I_1/I_3) with the increase of SLS concentration in polymer/SLS and SLS solution. The CMC/CAC values of the SLS, PVP/SLS, and PVP-VA/SLS systems could be identified at the bending points of the I_1/I_3 ratio. (The polymer concentration is 3 mg/mL.)

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Besides self-assembling with each other, SLS could also assemble around the hydrophobic segments of polymers, therefore demonstrating an apparently lower CAC due to the existence of extra hydrophobic components from the polymers.[29] To quantitatively compare the impact of PVP and PVP-VA on the micellization of SLS, we calculated the free energy of SLS micellization in the presence of different polymers with eq 1, which is also referred to as the phase separation model:[29]

$$\Delta G^{\circ} \approx RT \ln(\mathrm{CMC}) \quad (1)$$

where ΔG° is the standard free energy of micellization per mole of surfactant, R is the ideal gas constant, and T is temperature.

Calculated by eq 1, we determined that 1 mol of PVP-VA or PVP K30 lowers the free energy of SLS micellization by 1.9RT or 1.8RT, respectively. The 0.1RT difference is presumably caused by the differences in the chemical structures of PVP and PVP-VA, which will be confirmed in the following sections.

3.3. Molecular Interaction between Sorafenib and the PVP-VA/SLS Aggregates Revealed by 1D ^{13}C NMR Spectra. In order to investigate the interaction mechanism between sorafenib and the PVP-VA/SLS aggregates, 1D ^{13}C NMR spectra of water solution containing PVP-VA, SLS, and different concentrations of sorafenib were collected. The chemical shifts of the carbonyl carbons on the VP groups (C1), the VA groups (C1′), and SLS alkyl carbon (C12) were compared as the concentration of sorafenib increased from 1 mg/mL to 3 mg/mL.

As shown by Table 2, the chemical shifts of the carbonyl carbons of VA groups (C1′) and those of the SLS C12 carbons

Table 2. Influence of Sorafenib on the ^{13}C Chemical Shifts of PVP-VA C1, C1′, and SLS C1, C12 Carbons

Sorafenib (mg/mL)	1	1.5	2	2.5	3
PVP-VA C1'	+0.04	+0.02	+0.04	+0.17	+0.13
PVP-VA C1	+0.01	-0.03	+0.03	0.00	-0.02
SLS C1	-0.03	-0.04	-0.06	-0.07	-0.07
SLS C12	-0.06	-0.07	-0.10	-0.13	-0.14

shifted significantly (>0.1 ppm) after sorafenib concentration reached 2.5 mg/mL and above. However, the chemical shifts of the carbonyl carbons of the VP groups (C1) and those of the SLS C1 carbons remained unchanged, indicating that sorafenib is preferably solubilized by the hydrophobic cores formed by the VA groups and the hydrophobic alkane tail of SLS. As a rough qualitative comparison, the calculated logP values of the VA and VP groups were −0.169 and −0.655, respectively. The fact that the VA groups are more hydrophobic could have contributed a stronger molecular interaction between PVP-VA and SLS thus induced the formation of PVP-VA/SLS aggregates at a lower concentration, with a stronger solubilization capability than the PVP/SLS aggregates.

3.4. Supersaturation Kinetics of Sorafenib in Different Polymers and Different Polymer/SLS Systems. The supersaturation kinetics of sorafenib in FaSSIF, with/without the presence of PVP or PVP-VA, was determined and is shown in Figure 4. In order to quantitatively compare the ability of PVP and PVP-VA in maintaining sorafenib supersaturation, "supersaturation parameter", a previously defined dimensionless parameter between 0 and 1,[25] was calculated for each polymer/SLS system, and is listed in Table 3. As explained previously, a supersaturation parameter approaching 0 or 1 indicates no or very strong supersaturation maintaining ability, respectively.

As shown in Figure 4 and Table 3, PVP, regardless of its concentration, is not effective in maintaining sorafenib supersaturation regardless of the initial drug supersaturation, as evidenced by the supersaturation parameters that approach 0 (between 0.09 and 0.14), even with a relatively high PVP concentration of 3 mg/mL. In contrast, PVP-VA significantly prolonged sorafenib supersaturation in FaSSIF, with supersaturation parameter approaching 1, especially when the PVP-VA concentration increased to 3 mg/mL. Again, the difference between PVP-VA and PVP lies in the VA groups, thus we reason that VA groups are the underlying mechanism contributing to the supersaturation of sorafenib. In another words, to make a good "parachute" for sorafenib, we need VA groups in the solution.

As shown earlier, PVP-VA and SLS have synergistic effect to solubilize sorafenib (Figure 2). We further investigated the ability of PVP-VA/SLS in prolonging the supersaturation of sorafenib in FaSSIF, as shown in Figure 5. Surprisingly, even with the coexistence of a relatively low concentration of SLS at 12.5 μg/mL, it appeared that PVP-VA was no longer able to maintain the supersaturation of sorafenib effectively as evidenced by a decreased supersaturation parameter of 0.88. When the SLS concentration increased to 0.3 mg/mL, the supersaturation parameter was greatly reduced to be 0.15.

3.5. Investigation of the Specific Interaction between PVP-VA and SLS. Aforementioned data indicated that a certain kind of molecular interaction between PVP-VA and SLS played a critical role in improving the solubility of sorafenib; yet at the same time, this interaction also jeopardized the ability of PVP-VA to maintain a high level of supersaturation. In order to reveal the exact physical nature of this molecular mechanism, we investigated the PVP-VA/SLS solution using NOESY and ^{13}C NMR experiments.

3.5.1. NOESY. As a 2D NMR method, the cross peaks in NOESY connect the resonances from nuclei that are spatially close to each other,[30] thus to provide clear physical pictures regarding the spatial packing and interaction between different functional groups of PVP-VA and SLS. Figure 6A shows the NOESY spectrum of SLS (10 mg/mL) in the presence of PVP-VA (20 mg/mL); the peak assignments for each proton of SLS and PVP were made according to literature reports.[31] The NOESY spectrum clearly confirmed the existence of intermolecular interaction between the H4 protons of SLS (circled dots in Figure 6A), with either the position 2′ protons of the VA groups or the position 3 protons at VP groups, or both, because the chemical shifts of 2′ and 3 protons overlap with each other. As a comparison, the NOESY spectrum of SLS (10 mg/mL) and PVP (20 mg/mL) was collected and shown as Figure 6B, which showed no evidence of the existence of interaction between the SLS H4 proton with the position 3 protons at the VP groups, because there were no cross peaks at the corresponding positions (empty circles in Figure 6B).

Collectively, we conclude that, in the PVP-VA/SLS systems, SLS preferably interacts with the VA groups instead of the VP groups. This conclusion was further confirmed by the following solution NMR experiment.

3.5.2. 1D ^{13}C NMR Spectra. We investigated the effect of SLS on the ^{13}C NMR spectrum of PVP-VA (Figure 7). With the addition of SLS into the PVP-VA solution, the chemical shift of the VP carbonyl carbon (C1) of PVP-VA remains largely unchanged, in terms of either peak location or the peak

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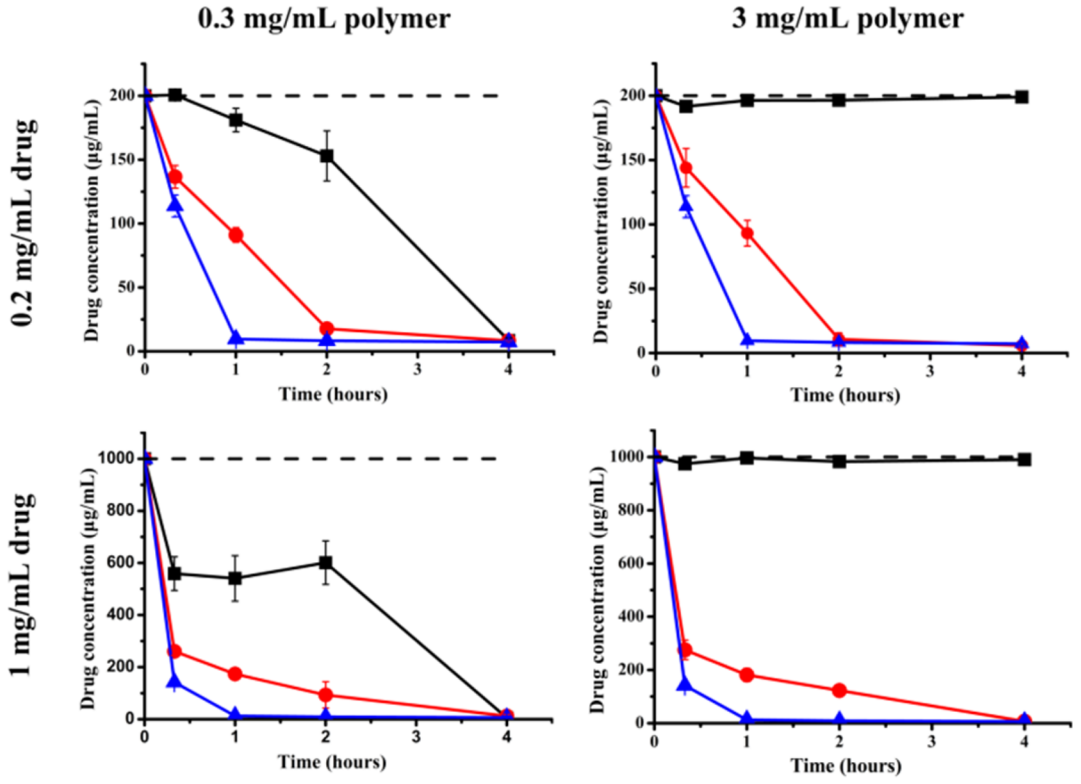

Figure 4. Effects of PVP-VA and PVP on the supersaturation of sorafenib in FaSSIF solution (n = 3, black ■, PVP-VA; red ●, PVP; blue ▲, without polymer). The initial supersaturated drug concentration is 0.2 or 1 mg/mL as illustrated by the dashed straight lines in each plot. The equilibrium solubility of crystalline sorafenib in FaSSIF solution is 3.3 μg/mL (too low to be displayed in these figures).

Table 3. Supersaturation Parameters[25] of Sorafenib in the Presence of PVP or PVP-VA

concn (mg/mL)		supersaturation param	
initial sorafenib	predissolved polymer	PVP-VA	PVP
0.2	0.3	0.59	0.13
	3.0	0.98	0.14
1.0	0.3	0.38	0.09
	3.0	0.99	0.10

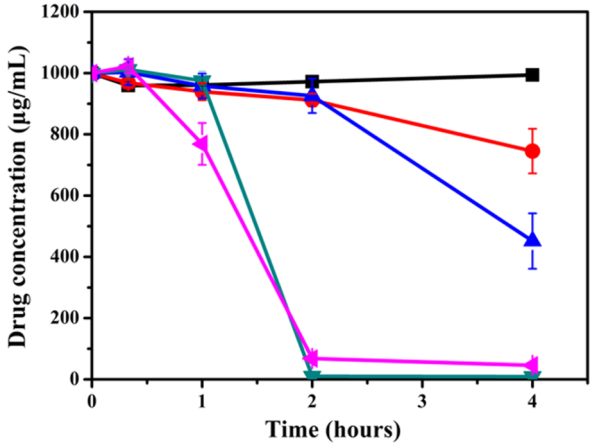

Figure 5. Supersaturation kinetics of sorafenib (initial concentration: 1 mg/mL) in FaSSIF solution in the presence of 3 mg/mL PVP-VA or a combination of 3 mg/mL PVP-VA and various concentrations of SLS (n = 3): black ■, PVP-VA only; red ●, PVP-VA and 12.5 μg/mL SLS; blue ▲, PVP-VA and 50 μg/mL SLS; green ▼, PVP-VA and 300 μg/mL SLS; pink ◀, PVP-VA and 1000 μg/mL SLS.

shape. In contrast, the chemical shift of the VA carbonyl carbon (C1′) shifted upfield with the increasing of SLS concentration. At the same time, the peak width of the C1′ chemical shift broadened gradually, indicating the restricted mobility of the VA groups due to the SLS interaction. This result further confirmed that SLS interacts with PVP-VA preferably through the VA groups, instead of the VP groups.

3.6. Investigation of the Specific Interaction between Polymer and Sorafenib. Figure 8 shows the carbonyl regions of the pure polymer, pure amorphous sorafenib, sorafenib/PVP-VA (Figure 8A), or sorafenib/PVP (Figure 8B) molecular level mixtures (prepared by co-spray drying), and physical blends of sorafenib/PVP-VA or sorafenib/PVP. In Figure 8A, two FT-IR peaks of pure PVP-VA centered at 1732 and 1668 cm^{-1} were assigned to the −C═O moieties of the VA groups and VP groups of PVP-VA, respectively; while in Figure 8B, the FT-IR peak of pure PVP centered at 1658 cm^{-1} was assigned as the −C═O moieties of the VP groups. Two FT-IR peaks centered at 1714 and 1654 cm^{-1} were assigned to the −C═O moieties of sorafenib.

In Figure 8A, there were two peaks in the spectrum of sorafenib/PVP-VA physical blend, at 1719 and 1657 cm^{-1}, respectively, corresponding to the VA and VP regions of PVP-VA. Interestingly, when the drug and polymer were intimately mixed, only the VA peak shifted significantly, from 1719 to 1734 cm^{-1}, while the VP peak only changed slightly from 1657 to 1659 cm^{-1}. In Figure 9B where VA groups are not present, the −C═O moieties of the physical blends was centered at 1655 cm^{-1}, which again only shifted slightly to 1659 cm^{-1} after PVP and sorafenib were mixed at molecular level. These FT-IR results again prove that sorafenib preferably interacts with the

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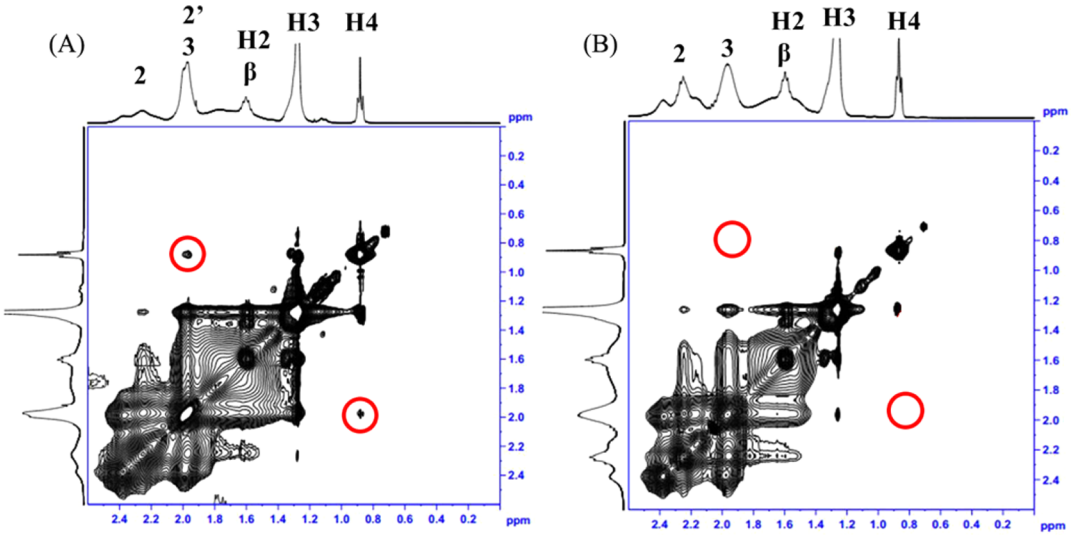

Figure 6. 1D ^{1}H NMR spectrum and contour plot of NOESY in D_2O system for (A) PVP-VA/SLS and (B) PVP/SLS systems. Both *x*-axis and *y*-axis represent the proton chemical shifts of polymer and SLS. The assignments of protons are shown in Figure 1.

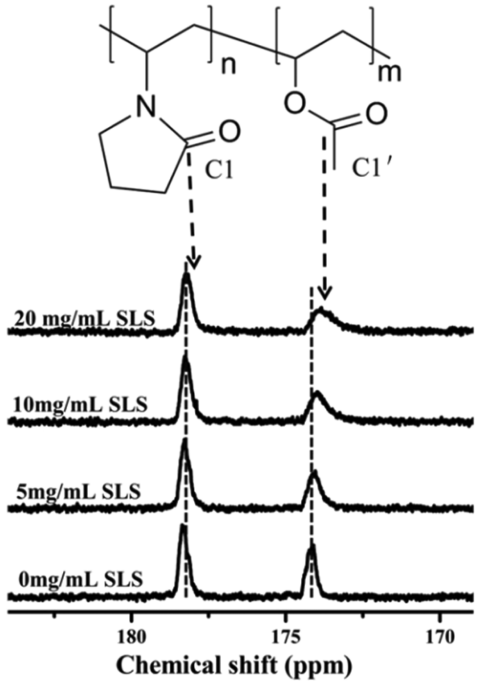

Figure 7. 1D ^{13}C spectra of 80 mg/mL PVP-VA in D_2O, titrated by increasing amount of SLS from 5 mg/mL to 20 mg/mL.

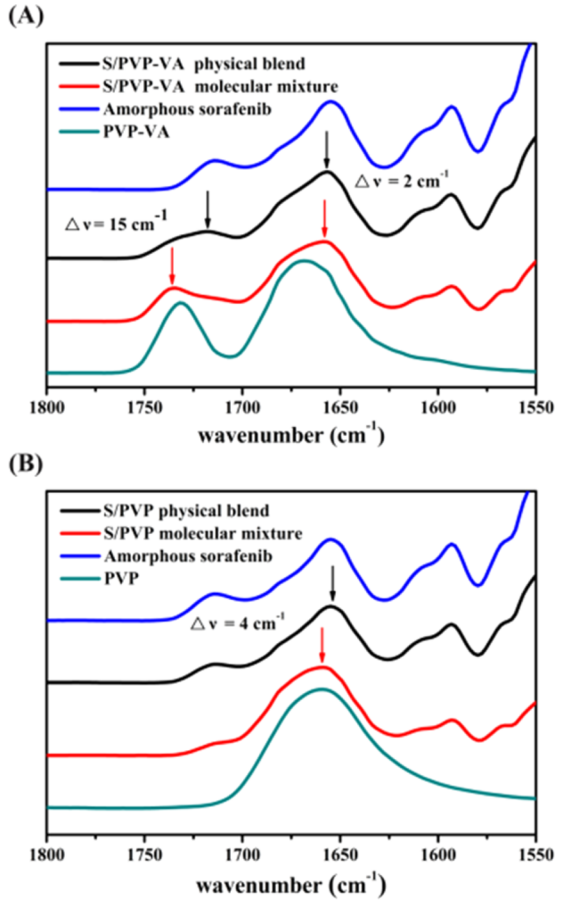

Figure 8. FT-IR spectra of the carbonyl regions for (A) 60/40 sorafenib/PVP-VA system and (B) 60/40 sorafenib/PVP system.

VA groups of PVP-VA, through some strong molecular interactions.

We also observed that sorafenib interacts with PVP-VA more strongly than PVP in aqueous solution. As shown in Figure 9, when an excess amount of sorafenib (dissolved in a small volume of DMSO) was introduced into water with predissolved PVP-VA or PVP (0.3 mg/mL), sorafenib crystallized and precipitated rapidly. When monitoring the change of polymer concentration in the solution, we noticed that PVP-VA concentration decreased significantly from 0.3 mg/mL to 0.186 mg/mL while PVP concentration of PVP showed no decrease at all. We reason that the strong molecular interaction between sorafenib and PVP-VA through the VA groups not only ensures PVP-VA to interact with any potential sorafenib aggregates but also leads to the disruption of the reorganization of the solute clusters,[32] and possibly, inclusion of PVP-VA into the sorafenib dominated precipitates. Polymers could affect nucleation by hindering the reorganization of a cluster of solute molecules into an ordered structure, which was believed to be the rate-limiting step of the two-step nucleation model.[21] Therefore, PVP-VA, but not PVP, is a potent nucleation

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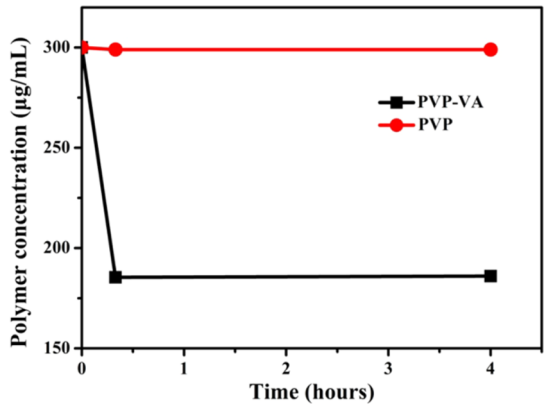

Figure 9. Effects of sorafenib on the polymer concentration after supersaturation study in water (n = 3). (The initial drug and polymer concentrations were 1 and 0.3 mg/mL respectively.)

inhibitor for sorafenib and can effectively maintain the supersaturation of sorafenib in aqueous medium.

3.7. Intrinsic and USP II Dissolution of Sorafenib Tablets Containing PVP-VA, SLS, or PVP-VA/SLS. Combining our findings discussed in sections 3.3 to 3.6, we can make several conclusions: (1) Sorafenib is mainly solubilized by the hydrophobic cores formed by the VA groups and the hydrophobic alkane tails of SLS. (2) SLS interacts preferably with the VA groups of PVP-VA, instead of the VP groups. (3) The supersaturation of sorafenib is mainly maintained by the VA groups of the PVP-VA. (4) SLS and sorafenib competitively interact with the VA groups of PVP-VA. Therefore, the addition of SLS reduced the ability of PVP-VA to sustain sorafenib supersaturation at high concentration, although the synergy between SLS and PVP-VA enhances the sorafenib solubility. We believe that utilizing PVP-VA and SLS appropriately in the sorafenib formulation could achieve the optimal "spring and parachute" effect, thus to maximize the bioavailability. To this end, we prepared three tablet formulations that contain PVP-VA alone, SLS alone, or both PVP-VA and SLS (Table 1), and compared their dissolution performance and also their *in vivo* pharmacokinetic in dogs (section 3.8).

The initial intrinsic dissolution rates of the tablets, or the "spring rates", were determined and are listed in Table 4. The tablet containing both PVP-VA and SLS (formulation C) showed the highest value of 190.5 μg cm^{-2} min^{-1}, much higher than formulation A (PVP-VA alone, 35.9 μg cm^{-2} min^{-1}) and formulation B (SLS alone, 5.9 μg cm^{-2} min^{-1}). It needs to be noted that sorafenib tosylate, instead of sorafenib free base, was used in the tablet formulation. Therefore, although SLS increases the solubility of sorafenib more than PVP-VA (section 3.1), the kinetic solubility of the salt form, plus the "parachute effect" of PVP-VA, contributed to the higher initial dissolution rate of formulation A. In the USP II dissolution (Figure 10), formulation A and formulation B demonstrated similar initial sorafenib dissolution rate (i.e., the slope of the initial dissolution phase), while formulation C again showed the highest initial dissolution rate.

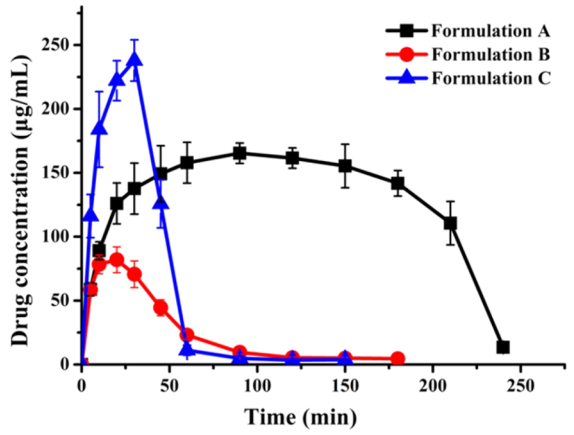

Figure 10. USP II dissolution profiles of three different formulations in FaSSIF solution (n = 3). The compositions of the three formulations are listed in Table 1.

When it comes to the "parachute time" (see Table 4 for definition) that different formulations demonstrated in the USP II study, the best performing formulation was formulation A, with a "parachute time" of 3.67 h. Both formulations B and C showed much shorter "parachute time" of 42 and 40 min, respectively, presumably due to the absence of PVP-VA or the presence of SLS. As we discussed earlier, SLS competitively binds on the VA groups of PVP-VA, thus negating the ability of PVP-VA to inhibit sorafenib crystallization through molecular interaction with VA groups. When using the dissolution performance parameter[25] to compare these three tablet formulations, formulation A is the best performing formulation (0.4), followed by formulation C (0.12), and formulation B performance the worst (0.06).

3.8. Compare the *in Vivo* Pharmacokinetic Performance of Sorafenib Tables Containing PVP-VA, SLS, or PVP-VA/SLS. As shown in Figure 11, the *in vivo* PK performance of the sorafenib tablets correlated well with the USP II dissolution results. The sorafenib tablets containing PVP-VA alone (formulation A) performed the best, followed by formulation C (PVP-VA and SLS). Formulation B showed the lowest bioavailability. Compared with formulation B, formulation A showed substantially improved C_{max} (1.85-fold) and AUC (1.79-fold). Although the coexistence of PVP-VA and SLS improved the equilibrium solubility of sorafenib ~50 times and the initial dissolution rate of sorafenib tablet, the presence of SLS significantly reduced the ability of PVP-VA in maintaining sorafenib supersaturation. Consequently, although formulation C demonstrated improved C_{max} and AUC

Table 4. USP II *in Vitro* Dissolution and *in Vivo* Performance of the Three Tablet Formulations

formulation	spring rate[a] (μg·cm^{-2} min^{-1})	parachute time[b] (min)	dissolution performance param[c]	*in vivo* performance (AUC, μg/mL[a]h)
A (PVP-VA)	35.9	220	0.4	64.8
B (SLS)	5.9	42	0.06	36.2
C (PVP-VA + SLS)	190.5	40	0.12	45.8

[a]Defined as the intrinsic dissolution rate of the tablet. [b]Defined as the peak width at half-height of the dissolution curve. [c]Dissolution performance parameter, defined in detail in ref 23. Briefly, it is a ratio between the AUC of the *in vitro* dissolution profile and the theoretical maximal AUC.

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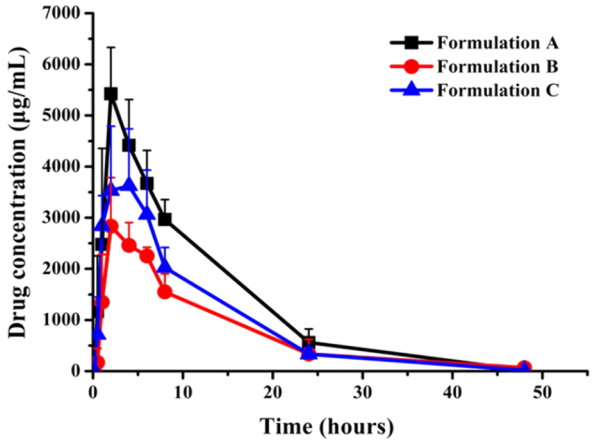

Figure 11. *In vivo* pharmacokinetic performance of three sorafenib tablet formulations (n = 3).

compared with formulation B, its bioavailability is lower than that of formulation A. This *in vivo* result demonstrated a good *in vivo* relevance of the molecular interaction mechanisms between sorafenib, PVP-VA, and SLS.

One intriguing discrepancy between the *in vitro* and *in vivo* performance is that, although these tablet formulations showed different T_{max} in the *in vitro* dissolution study, the *in vivo* T_{max} of these tablets appeared to be very similar. One plausible explanation is that the shear force generated by the gastrointestinal tract movement could have eliminated the difference in the disintegration behavior of these tablets, thus inducing their similar *in vivo* T_{max}.

4. CONCLUSION

Based on our study, we conclude that the solution behavior of sorafenib is critically controlled by the interactions between the drug, the coexistent polymer (PVP-VA or PVP), and surfactant (SLS). Equilibrium solubility of sorafenib can be enhanced significantly by the PVP-VA/SLS self-assembled complexes. Therefore, formulating with PVP-VA and SLS offered increased initial dissolution rate, or "spring rate" of sorafenib. Furthermore, through a strong molecular interaction with the PVP-VA VA groups, supersaturation of sorafenib could be well preserved by PVP-VA. Therefore, PVP-VA also serves as an effective "parachute" to maintain the supersaturation of sorafenib. At the same time, since SLS competes with sorafenib to interact with the same PVP-VA VA groups, the existence of SLS undercut the ability of PVP-VA to maintain sorafenib supersaturation. The net outcome of these interplays between drug, polymer, and surfactant was that formulation with only PVP-VA outperformed formulation with both PVP-VA and SLS, or formulation with SLS only, in both *in vitro* dissolution and *in vivo* bioavailability studies.

Although polymer−surfactant interaction was previously observed in several systems,[33,34] this research demonstrated that drug also plays a critical role among these interactions, and more significantly, these molecular interactions have evident impact on the *in vitro* and *in vivo* performance of an oral formulation. To maximize the oral bioavailability of a poorly water-soluble drug, the interactions between drug, polymer, and surfactant must be thoroughly investigated; and careful considerations of both "spring" and "parachute" phases of drug release process are critically necessary. Although it would be ideal to have both phases optimized simultaneously with formulation design, the reality might force us to find a balance between them (like the case discussed in the current paper). It is worth noting that the balance between the "spring" and "parachute" phases is highly dependent on the rate limiting steps during the drug absorption process, which are compound dependent. Compound properties such as permeability, absorption window, crystallization tendency, etc. should all be taken into account for the formulation design.

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Notes

The authors declare no competing financial interest.

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